citoxlab
Safety and Health Research

SYN549522

SYN549522 SC (A22011B) - Primary Skin Irritation Study in Rabbits

Final Report

DATA REQUIREMENT(S): OECD 404 (2015)
EPA 870.2500 (1998)
EC No 440/2008, B.4 (2008)

AUTHOR(S): Máté Weisz, M.Sc.

COMPLETION DATE: 16 January 2019

PERFORMING LABORATORY: Citoxlab Hungary Ltd.
H-8200 Veszprém, Szabadságpuszta,
Hungary

LABORATORY PROJECT ID: Report Number: 18/212-006N
Study Number: 18/212-006N
Task Number: TK0317170

SPONSOR(S): Syngenta Ltd.
Jealott's Hill International Research Centre
Bracknell, Berkshire, RG42 6EY, United Kingdom

VOLUME 1 OF 1 OF STUDY

STATEMENT OF DATA CONFIDENTIALITY CLAIMS

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GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

This study has been performed in accordance with the Principles of Good Laboratory Practice (Hungarian GLP Regulations: 42/2014. (VIII. 19.) EMMI decree of the Ministry of Human Capacities which corresponds to the OECD GLP, ENV/MC/CHEM (98) 17.).

This study was conducted in accordance with a written Study Plan, authorised by the Sponsor and Citoxlab Hungary Ltd. Management, and followed applicable Standard Operating Procedures.

I, the undersigned, declare that this report constitutes a true record of the actions undertaken and the results obtained in the course of this study.

Signature: _____ Date: 16 January 2019

Máté Weisz, M.Sc.
Study Director

Performing Laboratory: Citoxlab Hungary Ltd.
H-8200 Veszprém, Szabadságpuszta,
Hungary

FLAGGING STATEMENT

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QUALITY ASSURANCE STATEMENT

Study Number: 18/212-006N

Study Title: SYN549522 SC (A22011B) -
Primary Skin Irritation Study in Rabbits

Test Item: SYN549522 SC (A22011B)

This study has been inspected, and this report was audited by the Quality Assurance Unit, in compliance with the Principles of Good Laboratory Practice. As far as it can be reasonably established, the methods described and the results incorporated in this report accurately reflect the raw data produced during this study.

All inspections, data reviews and the report audit were reported in written form to the Study Director and to Management. The dates of such inspections and of the report audit are given below:

Date of Inspection	Phase(s) Inspected/Audited	Date of report to	
		Management	Study Director
10 October 2018	Study Plan	10 October 2018	10 October 2018
16 October 2018	Treatment	16 October 2018	16 October 2018
06 December 2018	Draft Report	06 December 2018	06 December 2018
16 January 2019	Final Report	16 January 2019	16 January 2019

Signature: Merazga Leila Date: 16 January 19

Leila Merazga, M.Sc.
On behalf of QA

MANAGEMENT STATEMENT

According to the conditions of the research and development agreement between Syngenta Ltd. (as Sponsor) and Citoxlab Hungary Ltd. (as Test Facility) the study titled "SYN549522 SC (A22011B) - Primary Skin Irritation Study in Rabbits" was performed, in compliance with the Principles of Good Laboratory Practice.

Signature: _____ Date: 16 Jan 2019

Alyson Leyshon, M.Sc.
Managing Director

GENERAL INFORMATION

Contributors

The following contributed to this report in the capacities indicated*:

Name	Function
Máté Weisz, M.Sc.	Study Director
Ádám Appl, M.Sc.	Assistant Scientist
Szabolcs Gáty, M.Sc.	Senior Director of Quality Assurance Unit
Leila Merazga, M.Sc.	Deputy Head of Quality Assurance Unit
László Székelyhidi, D.V.M.	Veterinary Control
Tamás Mészáros, Ph.D.	Pharmacy
Monique Trevisan Inforzato	Syngenta Study Manager

**Other trained, competent personnel may have worked on the study as required.*

Study dates

Study Initiation date:	11 October 2018
Experimental starting date:	16 October 2018
Experimental completion date:	21 October 2018
Receipt of animals:	03 October 2018
Acclimation:	03 – 15/17 October 2018
Treatment:	16 October 2018 (animal no. 2431) 18 October 2018 (animals no. 2827, 2430)
Observation of local findings:	For 72 hours after treatment. (16 – 19 / 18 – 21 October 2018)

Deviations from the guideline

There were no deviations during the study.

Performing laboratory test substance reference number

180275

Other

The study documents and samples:
- Study Plan,
- all raw data,
- sample of the test item,
- original Study Report and any amendments,
- correspondence

will be archived according to the Hungarian GLP regulations and to applicable SOPs in the archives of Citoxlab Hungary Ltd. 8200 Veszprém, Szabadságpuszta, Hungary.

After the retention time of 15 years has elapsed all the archived materials listed above will be returned to the Sponsor or retained for a further period if agreed by a contract. Otherwise the materials will be discarded.

TABLE OF CONTENTS

1.0 EXECUTIVE SUMMARY

1.1 Study Design

The primary skin irritation potential of SYN549522 SC (A22011B) was investigated according to the following guidelines; OECD 404 (2015), OPPTS 870.2500 (1998) and EC No 440/2008, B.4 (2008). Three young adult New Zealand rabbits were treated by topical, semi-occlusive application of 0.5 mL test item to their intact shaved back. The duration of treatment was 4 hours. The scoring of skin reactions was performed at approximately 1, 24, 48 and 72 hours after removal of the dressing. The primary irritation index (P.I.I.) was calculated by totalling the mean cumulative scores at 24, 48 and 72 hours and then dividing by the number of data points.

1.2 Results

The primary irritation index was 0.00.

The treated skin surface was examined at 1, 24, 48 and 72-hour after patch removal.

No local dermal signs were observed in the treated animals at 1, 24, 48 and 72-hour after patch removal through to the end of the observation period.

No clinical signs of systemic toxicity were observed in the animals during the study, and no mortality occurred.

As no clinical signs were observed at 72-hour after patch removal, the study was terminated after 72 hours of observation of the second and third rabbits.

The body weights of all rabbits were considered to be within the normal range of variability.

1.3 Conclusion

The application of SYN549522 SC (A22011B) did not result in any signs of skin irritation.

According to the Draize classification criteria, SYN549522 SC (A22011B) is considered to be “non-irritant” to rabbit skin (P.I.I. = 0.00).

2.0 INTRODUCTION

2.1 Purpose

The purpose of this primary skin irritation study was to assess the irritation potential of SYN549522 SC (A22011B) from a single dose placed on the skin of rabbits for 4 hours.

This study provides a rational basis for hazard classification.

The New Zealand white rabbit has been shown to be a suitable model for this type of study and is recommended in the test guideline. The results of the study are believed to be of value in predicting the likely skin irritancy potential of the test material to man.

Based on an *in vitro* skin irritation study (Orosz, 2018) that was conducted using the EpiSkin^{TM} model with SYN549522 SC (A22011B) (Batch number: SMU7JP001) the test item is indicated to be non-irritant. Since the test item was considered unlikely to cause severe skin irritation or skin damage, the *in vivo* study could be conducted for classification of skin irritation.

The study was designed such that the minimum number of animals were used. The test item was administered at 0.5 mL/animal, the dose specified in the test guidelines for a liquid test item.

2.2 Guidelines

The study was conducted according to the following guidelines:

- OECD Guidelines for Testing of Chemicals, Section 4, Number 404 “Acute Dermal Irritation / Corrosion”, adopted July 28, 2015.

- United States Environmental Protection Agency, Health Effects Division Test Guidelines, OPPTS 870.2500 Acute Dermal Irritation EPA 712-C-98-196, August 1998.

- Commission Regulation (EC) No 440/2008, B.4 (L 142, 30 May 2008).

2.3 Test Facility

This study was performed in an AAALAC-accredited laboratory. The Institutional Animal Care and Use Committee (IACUC) of Citoxlab Hungary Ltd. reviewed the Study Plan and authorised the conduct of the study.

3.0 MATERIALS AND METHODS

3.1 Test Substance

The following information was provided by the Sponsor.

Name:	SYN549522 SC (A22011B)
Batch number:	SMU7JP001
Active ingredient content*:	SYN549522 (a mixture of SYN547386 and SYN548941), 38.1% w/w corresponding to 448 g/L SYN547386, 34.3 % w/w corresponding to 403 g/L SYN548941, 3.83 % w/w corresponding to 45.0 g/L
Density:	1175 kg/m^3
Appearance:	Beige liquid
Recertification date:	30 November 2020
Storage conditions:	Room temperature (<30°C)
Safety precautions:	Routine safety precautions (lab coat, gloves, safety glasses, face mask) for unknown materials were applied to assure personnel health and safety.

*No correction for active ingredient content was applied.

The pH of the test item was measured and was found to be 6.0.

The Certificate of Analysis is shown in Appendix 1.

The integrity of supplied data relating to the identity, purity and stability of the test material is the responsibility of the Sponsor.

3.1.1 Identification and receipt

The test item of a suitable active ingredient content together with all precautions required in the handling and disposal of the test item were supplied by the Sponsor. The identification of the test item was made in the Pharmacy of Citoxlab Hungary Ltd. on the basis of the information provided by Sponsor.

3.1.2 Formulation

The test item was applied undiluted as supplied by the Sponsor.

3.2 Experimental Design

3.2.1 Animals

Species and strain:	New Zealand White Rabbit
Source:	S&K-LAP Kft. 2173 Kartal, Császár út 135, Hungary
Number of animals:	3
Sex:	Male
Age when treated:	Young adult, ~11 weeks
Body weight at dosing:	3028 g – 3360 g
Identification:	The animals were identified by engraved ear tags. The cages were marked with individual identity cards with information about study code, sex, cage number, dose and individual animal number.
Acclimation:	Under laboratory conditions after health examination. Only animals without any visual signs of illness were used for the study.
Acclimation time:	13 or 15 days

3.2.2 Husbandry

Animal health:	Only healthy animals were used for the study, as certified by the staff Veterinarian.
Room number:	033
Housing / Enrichment:	Animals were housed individually in AAALAC approved metal wire rabbit cages. Cages are of an open wire structure, and cages are placed together to allow some social interaction with rabbit(s) in adjoining cages.
Lighting periods:	12 hours daily, from 6.00 a.m. to 6.00 p.m.
Temperature:	19.9 – 22.8 °C
Relative humidity:	36 – 67 %
Ventilation:	15-20 air exchanges/hour.

The temperature and relative humidity values were measured continuously. The measured range was checked regularly during the acclimation and experimental phases.

3.2.3 Food and feeding

The animals received UNI diet for rabbits produced by Cargill Takarmány Zrt., *ad libitum*. The batch numbers of the lots used in the study were as follows:

- Batch number: 0005195239, expiry date: 10 November 2018,
- Batch number: 0005279068, expiry date: 21 December 2018.

The food was considered not to contain any contaminants that could reasonably be expected to affect the purpose or integrity of the study. A detailed description of the contents of the lots used is archived with the raw data at Citoxlab Hungary's Ltd.

3.2.4 Water supply and quality control

The animals received tap water, fit for human consumption, *ad libitum*, from the automatic system supplied by the communal water network. The water was considered not to contain any contaminants that could reasonably be expected to affect the purpose or integrity of the study.

The quality control analysis is performed at least once every three months, and microbiological assessment is performed monthly by Veszprém County Institute of State Public Health and Medical Officer Service (ÁNTSZ, H-8201 Veszprém, József Attila u.36., Hungary). Copies of the relevant Certificates of Analysis are retained in the archives at Citoxlab Hungary Ltd.

3.3 Administration of the Test Item

According to EC 2004/73, B.4. and OECD Guidelines 404, a test item does not need to be tested if the pH-value is equal/less than 2 or equal/greater than 11.5, owing to its predictable corrosive properties. The pH of the test item was measured before the study initiation date and was found to be 6.0.

Approximately 24 hours prior to the test, the hair was clipped from the back of the animals with an electric clipper, exposing an area of approximately 100 cm^2 (10 cm x 10cm).

Animals with overt signs of skin injury or marked irritation which may have interfered with the interpretation of the results were not used in the test.

On the day of treatment, 0.5 mL of test item was placed on a surgical gauze pad (*ca*. 2.5 cm x 2.5 cm). This gauze pad was applied to the intact skin of the clipped area and was kept in contact with the skin by a patch with a surrounding adhesive hypoallergenic plaster. The entire trunk of the animals was then wrapped with plastic wrap held in place with an elastic stocking.

The duration of treatment was 4 hours. The dressing was then removed and the skin was flushed with lukewarm tap water to clean the application site.

Initially, a single animal was treated. As neither a corrosive effect nor a severe irritant effect were observed after the 24-hour observation, the test was completed using the 2 remaining animals with an exposure period of 4 hours.

Clinical signs, including viability/mortality, were recorded daily from the day of application of the animals to the termination of the test.

Body weights were recorded on the day of application and at the end of the observation period.

3.4 *Post Mortem* Investigations

At the end of the observation period, animals were euthanised by intramuscular injections of Ketanest (Ketamine 10%) and Nerfasin (Xylazine 2%) followed by i.v. pentobarbital sodium anaesthesia. Following confirmation of death, the carcasses were discarded without further examination. Details of materials employed for euthanasia are retained in the raw data and detailed in Section 3.4.1.

3.4.1 Materials used for euthanasia

Name: Ketanest (100 mg/mL ketamine)
Batch No.: J4213-06
Expiry Date: 31 October 2020
Produced by: bela-pharm GmbH & Co. KG, Lohner Straße 19, D-49377 Vechta, Germany

Name: Nerfasin (20 mg/mL xylazine)
Batch No.: 16A134
Expiry Date: 31 December 2018
Produced by: Le Vet B.V., Wilgenweg 7, 3421 TV Oudewater, The Netherlands

Name: Euthanimal 40% (400 mg/mL pentobarbital sodium)
Lot No.: 1609291-03
Expiry Date: 31 October 2019
Produced by: Alfasan Nederland BV, Kuipersweg 9, Woerden, The Netherlands

3.5 Data Evaluation

The skin reaction was assessed according to the numerical scoring system listed in the Commission Directive 2004/73/EC, April 29, 2004 which was based on the Draize scoring system. The skin reaction was assessed at approximately 1, 24, 48 and 72 hours after the end of exposure (removal of the dressing, gauze patch and test item).

Summarised in tables, data reported included the irritation scores for erythema and oedema for each individual animal at all measurement intervals. Lesions, if observed, were described by the degree and nature of irritation, corrosion or any other toxic effects, and their reversibility.

The mean score was calculated across 3 scoring times (24, 48 and 72 hours after patch removal) for each animal for erythema/eschar grades and for oedema grades, separately. An

animal was positive when the mean score was 2 or greater. The test was positive for irritation when at least 2 animals were positive for the same endpoint (erythema/eschar or oedema).

The Cumulative Scores for the Skin Irritation Scores were calculated and represent the sum of all numerical scores for each animal at each time point. The resulting Mean Cumulative Skin Irritation Score was calculated for all animals at each time point.

The Primary Irritation Index (P.I.I.) was calculated by totalling the mean cumulative scores at 24, 48 and 72 hours and then dividing by the number of data points.

The irritation was classified according to the following criteria:

P.I.I. = 0	Not irritant
0 < P.I.I. ≤ 2	Mild irritant
2 < P.I.I. ≤ 5	Moderate irritant
5 < P.I.I.	Severe irritant

Viability/mortality, clinical signs and dermal findings were recorded on data sheets as appropriate.

Body weights were recorded on the day of the treatment and at the end of the observation period of each animal.

No statistical analysis was performed.

4.0 RESULTS AND DISCUSSION

4.1 Skin Irritation

Individual and mean skin irritation scores are presented in Tables 1 and 2. Individual local findings are shown in Appendix 2.

The primary irritation index was 0.00 (out of a maximum score of 8.0). No corrosive effects were noted on the treated skin of any animal at any of the observation intervals.

No local dermal signs were observed in the treated animals at the observation time points of 1, 24, 48 and 72-hour after patch removal.

4.2 Clinical Observations

No clinical signs of systemic toxicity were observed in the animals during the study, and no mortality occurred (Table 3).

4.3 Duration of the In-Life Phase

As no local or clinical signs were observed at 72-hour after patch removal, the study was terminated after the 72-hour observation time point of the second and third rabbits.

4.4 Body Weight

The body weights of all rabbits were considered to be within the normal range of variability (Table 4).

5.0 CONCLUSIONS

The application of SYN549522 SC (A22011B) did not result in any signs of skin irritation.

According to the Draize classification criteria, SYN549522 SC (A22011B) is considered to be “non-irritant” to rabbit skin (P.I.I. = 0.00).

6.0 REFERENCES

Orosz, I. (2018): SYN549522 SC (A22011B) - *In Vitro* Skin Irritation Test in the EPISKIN™ Model. Citoxlab Hungary Ltd. Study Code: 18/212-043B, Syngenta Task Number: TK0317170

Draize, J.H. (1959): Dermal Toxicity. In Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics, pp. 46-49. Austin, Texas: Association of Food and Drug Officials of the United States.

Draize, J.H., Woodward, G. & Calvery, H.O. (1944): Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. J. Pharmacol. Exper. Therap. 83: 377-390.

TABLES SECTION

GLOSSARY FOR TABLE 1

Grading of Skin Reactions

ERYTHEMA AND ESCHAR FORMATION

No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate to severe erythema	3
Severe erythema (beef redness) or eschar formation (injuries in depth preventing erythema) reading	4

OEDEMA FORMATION

No oedema	0
Very slight oedema (barely perceptible)	1
Slight oedema (edges of area well-defined by definite raising)	2
Moderate oedema (edges raised approximately 1 mm)	3
Severe oedema (raised more than 1 mm and extending beyond the area of exposure)	4

Primary Irritation Index (P.I.I.)

The irritation was classified according to the following criteria:

P.I.I. = 0	Not irritant
0 < P.I.I. ≤ 2	Mild irritant
2 < P.I.I. ≤ 5	Moderate irritant
5 < P.I.I.	Severe irritant

TABLE 1 Skin Irritation Scores - Individual Values

Animal Number	Sex	Evaluation Interval*	Erythema	Oedema	Cumulative	
					Score	Mean
2431	male	1 hour	0	0	0.00	0
2827	male		0	0	0.00	
2430	male		0	0	0.00	
2431	male	24 hours	0	0	0.00	0
2827	male		0	0	0.00	
2430	male		0	0	0.00	
2431	male	48 hours	0	0	0.00	0
2827	male		0	0	0.00	
2430	male		0	0	0.00	
2431	male	72 hours	0	0	0.00	0
2827	male		0	0	0.00	
2430	male		0	0	0.00	

* Examinations were performed at the specified times after removal of the dressing.

TABLE 2 Skin Irritation Scores - Mean Values after 24, 48 and 72 Hours

Animal Number	Sex	Erythema	N	Oedema	N	Primary Skin Irritation Index
2431	male	0	3	0	3	0.00
2827	male	0	3	0	3	
2430	male	0	3	0	3	
Mean score		0		0		

N= number of available data points.

TABLE 3 Clinical Signs

Animal Number	Sex	Observations	Observation time*				Frequency
			Day 0	Day 1	Day 2	Day 3	
2431	male	Symptom free	+	+	+	+	4/4
2827	male	Symptom free	+	+	+	+	4/4
2430	male	Symptom free	+	+	+	+	4/4
Remarks: + = present, Frequency: number of occurrence of observation/total number of observations *: relative to the day of treatment							

TABLE 4 Body Weights

Animal No.	Sex	Body weight (g)	
		Day of Treatment	End of observation period
2431	male	3360	3407
2827	male	3195	3241
2430	male	3028	3102

APPENDICES SECTION

APPENDIX 1 Certificate of Analysis

syngenta

Syngenta Crop Protection AG
GLP Testing Facility WMU
Analytical Development & Product Chemistry
Breitenloh 5
4333 Münchwilen, Switzerland

Certificate of Analysis

A22011B
SYN549522 SC (450)
SMU7JP001

Batch Identification	**SMU7JP001**
Other Batch ID	1013163
Product Code	**A22011B**
Other Product Code(s)	SYN549522 SC (450)
Chemical Analysis (Active Ingredient content)	
– **Identity of the Active Ingredient(s)***	**confirmed**
– **Content of SYN549522***	**38.1 % w/w corresponding to 448 g/l**
– **Content of SYN547386***	**34.3 % w/w corresponding to 403 g/l**
– **Content of SYN548941***	**3.83 % w/w corresponding to 45.0 g/l**
	The Active Ingredient(s) content is within the FAO limits.
Methodology used for Characterization / Recertification	HPLC, chiral HPLC, oscillating density meter
Physical Analysis	
– **Appearance**	**beige liquid**
– **Density***	**1175 kg/m³**
Stability:	
– **Storage Temperature**	**< 30 °C**
– **Recertification Date**	**End of November 2020**

If stored under the conditions given above, this test substance can be considered stable until the recertification date is reached.
This Certificate of Analysis summarizes data which originates either from a single study or from several individual studies. Tests marked with an asterisk (*) have been conducted in compliance with GLP.
Raw data, documentation, study plans, any amendments to study plans and reports pertaining to this/these study/studies are stored under the study number(s) referenced below within the archives of the GLP Testing Facility WMU at Syngenta Crop Protection AG, Switzerland.

Study number of batch characterization: CHMU170748
Study number(s) of batch recertification: ---

Authorization: 30-November-2017

Dr. Christian Mink
Analytical Development & Product Chemistry

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APPENDIX 2 Individual Local Findings

Animal No. 2431, Male

After 1 hour:	Erythema:	No abnormal findings noted
	Oedema:	No abnormal findings noted
	Flaking:	No abnormal findings noted
	Staining:	No staining presented
After 24 hours:	Erythema:	No abnormal findings noted
	Oedema:	No abnormal findings noted
	Flaking:	No abnormal findings noted
	Staining:	No staining presented
After 48 hours:	Erythema:	No abnormal findings noted
	Oedema:	No abnormal findings noted
	Flaking:	No abnormal findings noted
	Staining:	No staining presented
After 72 hours:	Erythema:	No abnormal findings noted
	Oedema:	No abnormal findings noted
	Flaking:	No abnormal findings noted
	Staining:	No staining presented

APPENDIX 2 Individual Local Findings (Continued)

Animal No. 2827, Male

After 1 hour:	Erythema:	No abnormal findings noted
	Oedema:	No abnormal findings noted
	Flaking:	No abnormal findings noted
	Staining:	No staining presented
After 24 hours:	Erythema:	No abnormal findings noted
	Oedema:	No abnormal findings noted
	Flaking:	No abnormal findings noted
	Staining:	No staining presented
After 48 hours:	Erythema:	No abnormal findings noted
	Oedema:	No abnormal findings noted
	Flaking:	No abnormal findings noted
	Staining:	No staining presented
After 72 hours:	Erythema:	No abnormal findings noted
	Oedema:	No abnormal findings noted
	Flaking:	No abnormal findings noted
	Staining:	No staining presented

APPENDIX 2 Individual Local Findings (Continued)

Animal No. 2430, Male

After 1 hour:	Erythema:	No abnormal findings noted
	Oedema:	No abnormal findings noted
	Flaking:	No abnormal findings noted
	Staining:	No staining presented
After 24 hours:	Erythema:	No abnormal findings noted
	Oedema:	No abnormal findings noted
	Flaking:	No abnormal findings noted
	Staining:	No staining presented
After 48 hours:	Erythema:	No abnormal findings noted
	Oedema:	No abnormal findings noted
	Flaking:	No abnormal findings noted
	Staining:	No staining presented
After 72 hours:	Erythema:	No abnormal findings noted
	Oedema:	No abnormal findings noted
	Flaking:	No abnormal findings noted
	Staining:	No staining presented

APPENDIX 3 Structured Study Summary

Structured Study Summary Table

Test substance design code	A22011B
Test substance batch code	SMU7JP001
Test substance purity (% w/w)	SYN549522 (a mixture of SYN547386 and SYN548941), 38.1% w/w corresponding to 448 g/L SYN547386, 34.3 % w/w corresponding to 403 g/L SYN548941, 3.83 % w/w corresponding to 45.0 g/L
Study number	18/212-006N
Study type	SKIN IRRITATION (DRAIZE)
Lab Reference	Citoxlab Hungary Ltd.
Study guidelines	OECD 404 (2015), OPPTS 870.2500 (1998), EC No 440/2008, B.4 (2008)
Nonstandard elements	-
Species	Rabbit
Strain	New Zealand White

Structured Study Results Table

Animal number	Clinical Observations	Mortality
2431	No clinical signs were observed	No
2827	No clinical signs were observed	No
2430	No clinical signs were observed	No

APPENDIX 4 GLP Certificate

OGYÉI
National Institute of
Pharmacy and Nutrition

H-1051 Budapest, Zrínyi u. 3.
1372 P.O. Box:450.
Tel: +36 1 88 69-300, Fax: +36 1 88 69 460
E-mail: ogyei@ogyei.gov.hu, Web: www.ogyei.gov.hu

Ref. no: OGYÉI/22762-5/2018
Admin.: Dr. Juhász Uzonka
Date: 03 August 2018

GOOD LABORATORY PRACTICE (GLP) CERTIFICATE

It is hereby certified that the test facility

CiToxLAB Hungary Ltd.

H-8200 Veszprém, Szabadságpuszta

is able to carry out

physico-chemical testing, toxicity studies, mutagenicity studies, environmental toxicity studies on aquatic or terrestrial organisms, studies on behaviour in water, soil and air; bio-accumulation, analytical and clinical chemistry, pathology studies, preparation of microscopic tissue sections, reproduction toxicology, in vitro studies, inhalation toxicology, and contract archiving

in compliance with the Principles of GLP (Good Laboratory Practice) and also complies with the corresponding OECD/European Community requirements.

Date of the inspection: **07-11 May 2018.**

Tarjáni Ibolya
Head of Inspectorate

Note: Translation of the Stamp on the official document ("Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet"): ("National Institute of Pharmacy and Nutrition")